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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,221	07/15/2003	Gary A. Koppel	41890-290023	8706

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/620,221	**Applicant(s)** KOPPEL, GARY A.	
	Examiner Leslie A. Royds Draper	**Art Unit** 1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 February 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2-6 and 11*.
   Claim(s) withdrawn from consideration: *1,7-10 and 12-17*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1614

Continuation of 3. NOTE: Applicant's proposed after-final amendment filed February 22, 2011 will not be entered into the record because the entry of such documents would require further consideration and/or search.

In particular, Applicant proposes narrowing the instant claims to those salts of clavulanic acid that are "pharmaceutically acceptable", in addition to proposing adding new limitations directed to administering clavulanic acid or a pharmaceutically acceptable salt thereof orally to a human patient in need of such treatment, which are considered new issues that would require additional consideration and/or search. As a result, entry of the proposed after-final submission would necessitate search and consideration of these new limitations in the claims, which is considered a new issue not previously considered. Accordingly, the amendments will not be entered into the record.

In addition, the proposed claim amendments are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal because they raise new issues that require further consideration and/or search. In addition, Applicant has added new claims without cancelling a corresponding number of finally rejected claims.

Continuation of 11. does NOT place the application in condition for allowance because:

Applicant's request for reconsideration of the present application with regard to the rejections and/or objections of record in light of the amendments to the claims proposed and presented in the after-final amendment has been made. In light of the fact that the proposed amendments to the claims will not be entered into the record, Applicant's remarks directed to the obviation of these rejections and/or objections as a result of the proposed amendments are not found persuasive.

Insofar as Applicant's remarks apply to the previously pending set of claims, the remarks have been fully and carefully considered, but are unpersuasive. Applicant states that Tew et al. fails to disclose any relationship between LpPLA2 and Alzheimer's disease, let alone any scientific or experimental data to support this alleged relationship, such that the artisan would not have predicted that an inhibitor of LpPLA2 could be used to treat the condition. Applicant cites to van Oijen et al., Chalbot et al., Koshy et al. and Levin to support his position that there is there was no correlation between LpPLA2 and dementia until after Tew et al. or the filing of the instant application.

These remarks are, and will remain, unpersuasive. Applicant's urgings that Tew et al. fails to provide data proving the correlation between LpPLA2 and Alzheimer's disease or data demonstrating efficacy or success in treating Alzheimer's disease with the clavulanic acid derivative compounds therein is tantamount to an allegation that Tew et al. is not enabled for the disclosed purpose. Such an argument contradicts the guidance provided in MPEP 2121.01[R-3], which states that, "A reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention. 'Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] knowledge the make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)." Thus, contrary to Applicant's assertions, the presumption of operability is not negated on the grounds that proof of efficacy such as, e.g., data, has not been provided in the reference. In addition, Tew et al. clearly provides adequate guidance to practice the invention without the need for undue experimentation by one of ordinary skill in the art for the reasons already made of record in the final rejection, which forecloses the argument that Tew et al. fails to provide enabling guidance for the method disclosed in the reference. In this case, the fact that Tew et al. may not provide a definitive exemplification of the compound(s) for treating Alzheimer's disease is an insufficient basis to conclude non-enablement of the reference when Tew et al. clearly provides adequate disclosure and guidance to place the claimed invention in possession of the public without the need to resort to undue experimentation.

Furthermore, the cited references fail to discredit this relationship between LpPLA2 and Alzheimer's disease as disclosed in Tew et al. Specifically, Applicant cites van Oijen et al. to support his position. However, the fact that the author believes he is the "first study to his knowledge" to show that LpPLA2 is associated with dementia is immaterial, since Tew et al. undoubtedly disclosed this relationship in his reference published in 1997. The fact that van Oijen et al. appears to be unaware of the prior teachings of Tew et al. does not invalidate the disclosure found in Tew et al. Furthermore, the recognition that the precise correlation between LpPLA2 and dementia requires further elucidation and scientific analysis does not diminish the importance of the clearly stated conclusion that there is an association between LpPLA2 and dementia. Further, Applicant cites to Chalbot et al. to show that sPLA2 was shown to be significantly increased in patients with Alzheimer's disease, but urges that sPLA2 is different than LpPLA2. This is unpersuasive. Chalbot et al. provides no discussion of the PLA2 isoform LpPLA2. The entire publication focuses on various PLA2 isoforms other than LpPLA2, whereas the focus of Tew et al. is the LpPLA2. Thus, Chalbot et al. fails to provide any basis to conclude that there is no relationship between the specific LpPLA2 isoform and the pathogenesis of Alzheimer's disease. In addition, it is noted that Applicant attempts to infer from the lack of discussion of LpPLA2 in Chalbot et al. that this enzyme is not involved in Alzheimer's disease. However, this conclusion is clearly without merit because the absence of evidence does not constitute evidence of absence. Thirdly, Applicant cites to Koshy et al. to show that Japanese patients with low levels of Lp-PLA2 do not exhibit a reduced risk of AD. However, note that Koshy et al. at p.779 clearly states that the results shown in the disclosed study must be interpreted within limits, in particular, that genetic deficiency of Lp-PLA2 activity could theoretically initiate compensatory mechanisms that alter the risk profile observed in epidemiological studies of Lp-PLA2 activity and the relationship between Lp-PLA2 and AD pathogenesis. Thus, the relationship between genetic deficiency of Lp-PLA2 expression and risk of Alzheimer's disease does not necessarily negate earlier findings that there is a relationship between high Lp-PLA2 activity and dementia. Moreover, even if, arguendo, Koshy et al. did definitively establish that low levels of Lp-PLA2 activity does not correlate to a reduced risk of Alzheimer's disease (which the Examiner does not concede), Koshy et al. was published after the filing date of the instant invention and, therefore, fails to demonstrate that, at the time of the instant invention, the art recognized that higher levels of Lp-PLA2 activity did not necessarily correlate to an increased risk of Alzheimer's disease.

Lastly, Applicant cites to a publication of Dr. Mark Levin to show that the link between Lp-PLA2 and Alzheimer's disease "remains unproven". However, while such a publication has been fully and carefully considered, this statement in the reference is unsupported by any

evidence and fails to be persuasive in this regard because it amounts to no more than an allegation without factual support, which is properly found unpersuasive in accordance with MPEP 2145.

For these reasons supra, the proposed amendments will not be entered into the record and the claims remain rejected for the reasons set forth in the final rejection dated October 19, 2010, of which said reasons are herein incorporated by reference.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1614